NON-TECHNICAL ABSTRACT

Alzheimer's disease is the most common cause of dementia, afflicting approximately 4.5 million Americans. Alzheimer's patients suffer a devastating decline in cognition and quality of life, and the disease represents a significant social and financial burden to society. In the Alzheimer's disease brain, cholinergic neurons in the basal forebrain structure known as the nucleus basalis of Meynert (NBM) die, and the loss of the cholinergic activity of these neurons has been correlated with the severity of dementia. Similarly, blockade of cholinergic neuron function is known to impair cognition in both humans and experimental animals, and conversely, today's standard of care medications for Alzheimer's disease, the cholinesterase inhibitors (ChEIs), alleviate symptoms by augmenting cholinergic function. However, while the ChEIs improve the function of remaining cholinergic neurons, they do not prevent the death of these neurons. Protecting these cholinergic neurons from degeneration and death, as well as enhancing their vitality, might be expected to slow the course of cognitive decline in Alzheimer's disease.

While it has been recognized for almost 20 years that neurotrophic proteins such as nerve growth factor (NGF) can both improve function and prevent the death of cholinergic neurons in experimental animals, a practical and safe method for delivering NGF to these neurons in humans has been lacking. Gene transfer (a.k.a. gene therapy) represents a potentially promising method for delivering NGF to the cholinergic neurons in the basal forebrain. In gene transfer, DNA encoding a protein is transferred to cells in an area where the protein is needed, and those cells use the transferred DNA to make the protein. While several methods of gene transfer exist, typically a gene transfer vector engineered from a virus is used. Virus-based gene transfer vectors utilize the natural capacity of viruses to transfer DNA (including genes) into cells. CERE-110 is a gene transfer vector engineered from adeno-associated virus (AAV). AAV is a virus that naturally infects human cells efficiently but does not cause any disease. In CERE-110, all of the AAV genes have been removed and replaced with the gene for NGF. Non-clinical research has established that CERE-110 efficiently transfers the NGF gene to the cholinergic neurons in the NBM. Following CERE-110 mediated transfer of the NGF gene to the NBM neurons, the NGF gene remains in the NBM neurons, and the NBM neurons then produce and secrete NGF. NGF acts locally in the NBM to enhance the vitality of cholinergic neurons, and to prevent them from dying.

The proposed clinical trial will investigate the safety and efficacy of administration of CERE-110 to the basal forebrain region containing the NBM in subjects with Alzheimer's disease. The trial is called "*A Phase I/II Dose-Escalating, Randomized, and Controlled Study to Assess the Safety, Tolerability, and Efficacy of CERE-110 [Adeno-Associated Virus-Based Gene Transfer Vector for the Delivery of beta-Nerve Growth Factor (NGF)] in Subjects with Mild to Moderate Alzheimer's Disease*". The Phase I portion of the study will evaluate 6 subjects, and the purpose will be to establish the safety of CERE-110 at two different doses. The blinded Phase II portion, which will evaluate 30 subjects, will continue to examine safety of CERE-110 but is also designed to give a preliminary indication of the effectiveness of CERE-110 for Alzheimer's disease.

In the Phase I portion of the study, the first 3 subjects will receive the lower of two doses of CERE-110, neurosurgically administered to their basal forebrain. In order to be cautious and allow sufficient time to monitor safety between subjects, the study will wait at least 4 weeks between each subject's surgery. If the low dose is found to be well tolerated, 3 subjects will receive the higher dose of CERE-110 in the same staggered fashion.

One month after the last subject receives CERE-110 in Phase I, if no safety concerns have arisen, the Phase II portion of the study will begin. In Phase II, two thirds of the subjects (randomly determined) will receive the highest safe dose of CERE-110 as determined from Phase I, and the other third of the subjects will undergo a sham surgical procedure as a control. The sham procedure will only open the skull, and will not involve any breach of the protective tissue (dura matter) covering the brain. To minimize bias and placebo effect, the

subject as well as the neurologists who perform the exams will not know (i.e., will be blinded to) which treatment the subject received. The effectiveness of CERE-110 will be determined by comparing performance of subjects who received CERE-110 to that of subjects who received only the sham surgery on various tests of cognitive function. Safety will be the primary objective of the study, and will be closely monitored throughout. Blood samples will be tested for the presence of CERE-110 and checked for antibodies to CERE-110 and NGF.

Subjects will be aged between 50 and 80 years old and able to provide informed consent. The primary enrollment criterion will be a diagnosis of mild to moderate Alzheimer's disease. Subjects will also have no other significant neurological or medical abnormalities contraindicating surgery or study participation. After completion of the study, all participants will undergo annual monitoring.